Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Virology

Public enemy number one

The new coronavirus is no small threat, but we are starting to understand how it works, reports **Michael Marshall**

THE covid-19 virus is humanity's newest foe, with the potential to prematurely end millions of lives. To control this new coronavirus, we need to understand it. Labs around the world are now working around the clock in a bid to know their enemy.

Three crucial questions are occupying virologists. What makes the new virus so good at infecting people? How does it reproduce so quickly once it is inside us? And why doesn't the virus cause symptoms straight away, allowing it to spread undetected? The answers will suggest ways to treat the disease and develop vaccines (see "Race for a vaccine", page 44). Clues can be found in the virus's biology.

Like all viruses, the covid-19 virus must infect living cells in order to reproduce. Each virus strives to burrow into a cell and take over its internal machinery, repurposing it to build the components of new viruses. These new viruses are then ejected from the cell, where they can infect more cells – either in the same body, or in a new host.

The covid-19 virus belongs to a family of coronaviruses, which are fairly intricate as viruses go. Each coronavirus has at its core a strand of RNA, a molecule similar to DNA that carries the virus's genes. Around this is a protein shell, which is surrounded by two layers of molecules called lipids. This outer membrane is dotted with proteins, some of which stick out like the spikes on a sea urchin.

The spike proteins are critical, says Michael Letko at the National Institute of Allergy and Infectious Diseases in Montana. They act as an anchor for the virus, attaching to a protein on the outside of a cell.

In a study published on 9 March, researchers led by Alexandra Walls at the University of Washington in Seattle used electron microscopy to determine the atomic structure of the spike protein on the covid-19 virus (*Cell*, doi.org/dpvh). With this information, inhibitor drugs can now be designed to block it from attaching to a human cell.

"The spike proteins are crucial. They act as an anchor for the virus to attach to the cell"

Another approach is to target the proteins on human cells that the spike proteins latch on to. To do that, we first have to know what they are. One candidate for this method is the attachment point used by the closely related SARS virus: angiotensin-converting enzyme 2 (ACE2). In late February, Letko's team became one of several to confirm that the new coronavirus's spike protein also binds to ACE2 (*Nature Microbiology*, doi.org/dpvk).

Letko says a role for ACE2 makes sense. "It's expressed in the lung and it's expressed in the gastrointestinal tract, so that may partially explain why the virus is able to infect those places."

However, the virus doesn't simply attach itself to ACE2. The spike protein first has to split itself, and it harnesses human cell proteins to do this. One protein that is co-opted in this way is transmembrane protease serine 2 (TMPRSS2), which was identified by two studies published in March (*Cell*, doi.org/ggnq74; *PNAS*, doi.org/dpvm). Walls's team found that a second protein called furin can also split the spike protein.

"These can also be targets," says Rolf Hilgenfeld at the University of Lübeck in Germany. If we can block these human proteins with drugs, the virus wouldn't be able to get into the host cell – although the proteins' normal functions would also be interrupted, potentially causing side effects.

The virus's entry into cells can also be interrupted by a protein called lymphocyte antigen 6E (LY6E), which is involved in our immune response. In a study published on 7 March, Stephanie Pfänder at Ruhr-University Bochum in Germany and her colleagues showed that LY6E stops many coronaviruses, including the covid-19 virus, from entering cells, and that mice lacking LY6E are more vulnerable to infection than those with it (bioRxiv, doi.org/dpvn).

She says that if we find out what this protein does, it might be possible to mimic it with a drug, and it may be able to fight against infection by many coronaviruses. "Having a [coronavirus] inhibitor would obviously be of great

No, this virus isn't a bioweapon

New diseases have emerged throughout human history, and we have seen two major coronavirus outbreaks in the last two decades: SARS and MERS. So we shouldn't be surprised by the arrival of the covid-19 virus.

However, rumours on social media suggest that the outbreak was human-made. Some say the virus leaked from a Chinese lab studying coronaviruses. Others suggest the virus was engineered to spread among humans.

Even the most secure laboratories do sometimes have accidents, and a human-engineered pandemic has been identified as a possible risk to our civilisation, but there is no good evidence that either has happened.

Many similar viruses are found in wild bats, and it seems likely that is the origin of this one, probably via an intermediate host. Similarly, we know that both SARS and MERS came from bats, so there is no reason to invoke a laboratory accident.

Researchers led by Shan-Lu Liu at the Ohio State University say there is "no credible evidence" of genetic engineering (*Emerging Microbes & Infections*, doi.org/dpvw). The virus's genome has been sequenced, and if it had been altered, we would expect to see signs of inserted gene sequences. But we now know the points that differ from bat viruses are scattered in a fairly random way, just as they would be if the new virus had evolved naturally.

SYLVAIN LEFEVRE/GETTY IMAGES

Labs around the world are racing to understand the new coronavirus

importance also to help against future outbreaks and not only the current pandemic," she says.

Stopping a virus entering cells is one thing, but if a person is already infected it may not help. In that case, we need a way to interfere with a virus's ability to copy itself inside cells.

There are two obvious attack points. To proliferate, the virus has to build proteins, and copy its RNA genome. The proteins are made first. When the virus's RNA enters an infected cell, the host machinery reads the virus's genes and strings together two large "polyproteins" containing several viral proteins. Some of these are enzymes called proteases, which first cut themselves out of the polyprotein, and then cut out other proteins, freeing them to carry out their functions.

"When you interrupt that, the virus cannot replicate," says Hilgenfeld. His team has determined the atomic structure of the main protease (bioRxiv, doi.org/dpvp) and identified substances that bind to it (bioRxiv, doi.org/dpvq).

His group has been developing an inhibitor for the main proteases of coronaviruses and a related group called enteroviruses in the hope that such a drug would be broadly applicable enough to appeal to a drug company. The researchers have now modified them so that they also work on the covid-19 virus and showed that the resulting drug works on single cells. However, there are still many more stages of testing before the drug could be used in people with covid-19.

The other option is to stop the virus copying its genome. This is done by another viral protein, the RNA-dependent RNA polymerase (RdRP). Most RNA viruses don't check for errors when copying their genomes, so they can be blocked by introducing modified RNA building blocks, which the RdRP will incorporate "if the virus is stupid enough", says Hilgenfeld.

Unfortunately, coronaviruses like the covid-19 virus have a proofreading enzyme called exonuclease, which removes the modified RNA components and allows copying to continue. "Many of the existing RdRP inhibitors do not help against coronaviruses," says Hilgenfeld.

Nevertheless, in a preliminary step, researchers led by Tai Yang at Chengdu Medical College in China have identified seven chemicals that calculations suggest might bind to it (*Preprints*, doi.org/dpvs). Meanwhile, a drug called remdesivir, originally developed to treat Ebola, has also shown promise as an RdRP inhibitor.

In the long term, we need to know why this virus is so good at spreading. "It's the undetected spread that's contributed a lot to the severity of this outbreak," says Letko.

The key to the virus's spread is its ability to reproduce inside our bodies for days without triggering our immune response. The most recognisable symptoms of covid-19 – fever and coughing – are actually due to our immune system fighting back – but the virus delays this with extra genes it carries.

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The number of outer lipid layers that protect the covid-19 virus

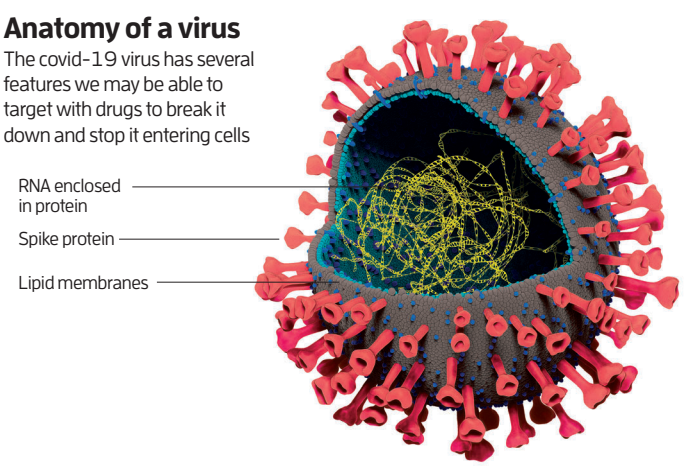
These "non-structural genes" code for proteins that interfere with our immune system. When a cell becomes infected, an alarm system called the interferon pathway is triggered. "The virus has proteins to interfere with that pathway," says Letko.

Some of the non-structural genes of the covid-19 virus look similar to known genes, so we can make an educated guess about their function. "But some of the stuff we really don't have a firm grasp on," says Letko.

In the immediate future, understanding these proteins may not help us slow the outbreak, but it could help us build antiviral drugs in the future. ▮

Anatomy of a virus

The covid-19 virus has several features we may be able to target with drugs to break it down and stop it entering cells



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